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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HUYNH, PHUONG N

ART UNIT PAPER NUMBER

1644

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/380,327

Applicant(s)

ROBERTSON ET AL.

Examiner

" Neon" Phuong Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 December 2002.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 50-60, 64-71, 73, 75-77, 79, 81 and 83-93 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

- 5) ☐ Claim(s) _____ is/are allowed.

- 6) ☒ Claim(s) 50-60, 64-71, 73, 75-77, 79, 81, and 83-93 is/are rejected.

- 7) ☐ Claim(s) _____ is/are objected to.

- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14. 6) ☐ Other: _____

DETAILED ACTION

1. The request filed on 12/23/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/380,327 is acceptable and a CPA has been established. An action on the CPA follows.
2. Claims 50-60, 64-71, 73, 75-77, 79, 81, and 83-93 are pending.
3. Claims 50-60, 64-71, 73, 75-77, 79, 81, and 83-93 are being acted upon in this Office Action.
4. The drawings, filed on 9/3/99, stand not in compliance with 37CFR 1.84(a). Please see attached PTO 948 mailed 3/14/01. Appropriate correction is required. It is noted that formal drawings will be submitted at a later time prior to or at payment of the issue fee. It is noted that Applicants will submit them in due course but no later than at the time of payment of the issue fee.
5. The disclosure stands objected to because the **amendment** to the abstract filed on 6/18/01 was not on a separate sheet as required by 37 CFR 1.72(b). All abstract must be on a separate sheet.
6. Claim 50 is objected to because "TGF β 1" is recited twice.
7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
8. Claims 50-60, 64-71, 73, 75-77, 79, 81, and 83-93 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of eliciting an immune reaction in a prospective mammalian mother to sperm antigens of a prospective father to alleviate symptoms of an infertility condition, said method comprising administering said prospective mother to said sperm antigens of said prospective father and to substantially purified TGF β , said method leading to tolerance to said sperm antigens and alleviation of said infertility condition, **does not** reasonably provide enablement for a method of alleviating symptoms of an infertility condition in any mammalian prospective mother comprising exposing the prospective mother to

(1) *any* one or more MHC Class I antigens of the prospective father, (2) *any* one or more antigens, (3) *any* one or more antigens are chosen as a result of being "particularly antigenic and prominent either on the sperm or the conceptus, (4) *any* one or more antigens are presented in purified or semi-purified form, (5) *any* TGF β is "modified", and (6) *any* TGF β wherein the modification "comprises" substitution, deletion, or addition mutant, or *any* peptide fragments of TGF β , thereby to induce tolerance to said one or more antigen or antigens.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses only a method of eliciting an immune response in a prospective mother to **sperm antigen** (antigens on the sperm) and MHC class I by co administering sperm antigen in the form of the prospective father's ejaculate and TGF β together before attempted conception (see page 7 line 35, Fig 9 of specification) or administering TGF β after intercourse (See page 8, line 4-5) to induce tolerance and for alleviate the symptoms of infertility conditions.

The specification does not teach how to make and use one or more of any antigen mentioned above because antigen without SEQ ID NO or the specific amino acid sequence has no structure, much less function, in turn, would be useful as a method for alleviating symptoms of an infertility condition in any mammalian prospective mother. Applicant has not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the antigen or antigens other than those encompassed by the sperm antigen or MHC class I molecule on the sperm in the form of ejaculate of the prospective father.

Ngo *et al.*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo *et al.*, 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). Given the indefinite number of undisclosed "antigens", there is insufficient working example demonstrating that any antigen is effective for induction of tolerance as a method alleviating symptoms of an infertility condition in any mammalian prospective mother. It is unpredictable which undisclosed

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antigens would be useful for induction of tolerance, in turn, for a method of alleviating the symptoms of infertility condition.

With regard to TGF β is "modified", *any* TGF β wherein the modification "comprises" substitution, deletion, or addition mutant, or any peptide fragments of TGF β as recited in claims 75 and 76, respectively, there is no guidance in the specification as filed regarding which amino acid within the full length of any TGF β 1, TGF β 2, TGF β 3 and activin can be modified such as addition, substitution, or deletion and whether the resulting TGF β after modification would retain both structure and biological activity. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality such as stimulates GM-CSF production requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. Not only there is a lack of guidance as to which amino acid within the full length TGF β can be modified, the term "comprising" is open ended. It expands the modification to include a combination of substitution, and deletion. There is a lack of working example to demonstrate that the modified TGF β would still be effective for induction of tolerance to any antigen or antigens to alleviate symptoms of infertility.

Mason *et al* teach that even one amino acid substitution such as cysteine for alanine (there were 9 of them in total) of activin A, which is a member of TGF β family fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular) or loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) or loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach that the equivalent in TGF β 1 in which the cysteine residue corresponding to residue 77 when changed to a serine residue, the resulting secreted monomer has no bioactivity (See page 330, column 1, first paragraph, in particular). Given the indefinite number of undisclosed modified TGF β , analog and fragment thereof, it is unpredictable which undisclosed modified TGF β would have the same function and structure as the full length TGF β such as such as TGF β 1, TGF β 2, TGF β 3 and activin, in turn, would be useful for any purpose. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any TGF β 1, TGF β 2, TGF β 3 and activin,

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having substitution, deletion or addition other than those defined by TGF β 1, TGF β 2, TGF β 3 and activin. Without sufficient guidance, the changes which can be made in the structure of "TGF β " and still provide immune suppressive function (induction of tolerance) is unpredictable and the experimentation left to those skilled in the art is unnecessarily, extensive and undue.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 6/14/01 have been fully considered but are not found persuasive.

Applicants' position is that (1) the amended claims specified that the TGF β which may be selected from the group consisting of TGF β 1, TGF β 2, TGF β 3 and activin. (2) A wide variety of fragments and analogues of various TGF β molecules are known and their sequences have been published as evidence by the paragraph 10 of the Declaration of David Clark. (3) Figures 4 of the specification clearly shows that both TGF β 1, and TGF β 2, in seminal plasma elicit GM-CSF stimulating activity. (4) Applicants have now obtained further experimental results, which clearly show that all three isoforms of TGF β are able to induce release of GM-CSF from human cervical keratinocytes.

However, the amended claims still recite any MHC class I antigen, any one or more antigens. The specification discloses only sperm antigen and MHC class I antigen expressed on the sperm, not just any antigen. The specification does not teach how to make and use one or more of any antigen mentioned above because antigen without SEQ ID NO or the specific amino acid sequence has no structure, much less function, in turn, would be useful as a method for alleviating symptoms of an infertility condition in any mammalian prospective mother. Applicant has not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the antigen or antigens other than those

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encompassed by the sperm antigen or MHC class I molecule on the sperm in the form of ejaculate of the prospective father.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo *et al*., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). Given the indefinite number of undisclosed "antigens", there is insufficient working example demonstrating that any antigen is effective for induction of tolerance as a method alleviating symptoms of an infertility condition in any mammalian prospective mother. It is unpredictable which undisclosed antigens would be useful for induction of tolerance, in turn, for a method of alleviating the symptoms of infertility condition.

Further, the amended claims still recite TGF β is "modified", *any* TGF β wherein the modification "comprises" substitution, deletion, or addition mutant, or any peptide fragments of TGF β as recited in claims 75 and 76, respectively, there is no guidance in the specification as filed regarding which amino acid within the full length of the member of TGF β family such as TGF β 1, TGF β 2, TGF β 3 and activin can be modified such as addition, substitution, or deletion and whether the resulting TGF β after modification would retain both structure and biological activity. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality such as stimulates G-CSF production requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. Not only there is a lack of guidance as to which amino acid within the full length TGF β can be modified, the term "comprising" is open ended. It expands the modification to include additional substitution, and deletion. There is a lack of working example to demonstrate that the modified TGF β would still be effective for induction of tolerance to any antigen or antigens to alleviate symptoms of infertility.

Mason *et al* teach that even one amino acid substitution such as cysteine for alanine (there were 9 of them in total) of activin A, which is a member of TGF β family fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular) or loss biological activity (See activin cysteine

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mutant 4 and 12, page 327, column 2, in particular) or loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach that the equivalent in TGF β 1 in which the cysteine residue corresponding to residue 77 when changed to a serine residue, the resulting secreted monomer has no bioactivity (See page 330, column 1, first paragraph, in particular). Given the indefinite number of undisclosed modified TGF β , analog and fragment thereof, it is unpredictable which undisclosed modified TGF β would have the same function and structure as the full length TGF β such as TGF β 1, TGF β 2, TGF β 3 and activin, in turn, would be useful for any purpose.

The specification as filed discloses only administering TGF β 1 and with sperm antigens of the prospective father to a prospective mother to induce tolerance as a method of alleviating symptoms of infertility. There are no additional modified TGF that "comprises substitution, deletion or addition mutants, analog or derivative thereof" in the specification, much less having the same function as TGF β such as TGF β 1, TGF β 2, TGF β 3 and activin. The declaration of David Clark and the enclosed review articles fail to shore up the deficiency of modified TGF β comprising substitution, deletion, or addition mutants, including *any* peptide fragments of TGF β for the claimed method.

9. Claims 50-60, 64-71, 73, 75-77, 79, 81, and 83-93 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method of alleviating symptoms of an infertility condition in any mammalian prospective mother comprising exposing the prospective mother to (1) *any* one or more MHC Class I antigens of the prospective father, (2) *any* one or more antigens, (3) *any* one or more antigens are chosen as a result of being "particularly antigenic and prominent either on the sperm or the conceptus, (4) *any* one or more antigens are presented in purified or semi-purified form, (5) *any* TGF β is "modified", and (6) *any* TGF β wherein the modification "comprises" substitution, deletion, or addition mutant, or *any* peptide fragments of TGF β , thereby to induce tolerance to said one or more antigen or antigens.

The specification discloses only a method of eliciting an immune response in a prospective mother to sperm antigens (antigens on the sperm) and MHC class I by co

administering sperm antigens in the form of the prospective father's ejaculate and TGF β together before attempted conception (see page 7 line 35, Fig 9 of specification) or administering TGF β after intercourse (See page 8, line 4-5) to induce tolerance and for alleviate the symptoms of infertility conditions. The specification discloses on page 8 at line 7 that the nature of the relevant surface antigens is not entirely clear but will presumably be those that are particularly antigenic and prominent either on the sperm or on the conceptus. The most likely candidates are MHC antigens and more preferably MHC class I. The surface antigens from the male parent may include leukocytes, the antigens may also be presented in biological fluids such as seminal plasma.

The term "antigen" without SEQ ID NO or the specific amino acid sequence has no structure, much less function, in turn, would be useful as a method for alleviating symptoms of an infertility condition in any mammalian prospective mother. The specification discloses only sperm antigen, MHC class I antigen on the sperm or leukocytes or in the seminal plasma. Applicant has not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the antigen or antigens other than those encompassed by the sperm antigen or MHC class I molecule on the sperm in the form of ejaculate of the prospective father.

With regard to TGF β is "modified", *any* TGF β wherein the modification "comprises" substitution, deletion, or addition mutant, or any peptide fragments of TGF β as recited in claims 75 and 76, respectively, there is inadequately written description about structure, much less about the function of any modified TGF β that "comprises" substitution, deletion, or addition mutant, and any peptide fragments of TGF β .

With the exception of the specific sperm antigen and the specific TGF β mentioned above, there is insufficient written description about **the structure associated with function** of *any* MHC class I antigens, *any* one or more antigens, *any* TGF β is modified, and *any* TGF β wherein the modification comprises substitution, deletion, or addition mutants, *any* peptide fragments of TGF β , and *any* derivative or analog thereof.

Given the lack of a written description of any additional species of MHC class I antigen, modified TGF β , analog and fragment thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398. Applicant is directed to the Revised Interim Guidelines for the

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Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 6/14/01 have been fully considered but are not found persuasive.

Applicants' position is that (1) the amended claims specified that the TGF β which may be selected from the group consisting of TGF β 1, TGF β 2, TGF β 3 and activin. (2) A wide variety of fragments and analogues of various TGF β molecules is known and their sequences have been published as evidence by the paragraph 10 of the Declaration of David Clark. (3) Figures 4 of the specification clearly shows that both TGF β 1, and TGF β 2, in seminal plasma elicit GM-CSF stimulating activity. (4) Applicants have now obtained further experimental results, which clearly show that all three isoforms of TGF β are able to induce release of GM-CSF from human cervical keratinocytes.

However, the issue is not TGF β 1, TGF β 2, TGF β 3 and activin. There is insufficient written description about *any* modified TGF β and *any* TGF β wherein the modification "comprises" substitution, deletion, or addition mutant, or *any* peptide fragments of TGF β . The specification merely mentioned modified TGF β comprising substitution, deletion, or addition mutants, *any* peptide fragments of TGF β . The term "modified TGF β comprising substitution, deletion, or addition mutants, *any* peptide fragments" does not convey the structure of said modified TGF β , let alone having similar function as unmodified TGF β such as TGF β 1, TGF β 2, TGF β 3 and activin, in turn, useful for induction of tolerance to any MHC class I antigen as a method of alleviating symptoms of an infertility condition.

Further, the amended claims still recite any MHC class I antigen, any one or more antigens. The specification discloses only sperm antigen, MHC class I antigen on the sperm or leukocytes or in form seminal plasma. The specification does not provide a sufficient enabling description of any antigens, any MHC class I antigen.

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10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 50-51, 60 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "mucosal surface" in claim 51 has no antecedent basis in base claim 50 because the base claim requires only exposing the prospective mother to one or more MHC Class I antigen of a prospective father.

The recitation of "being particularly antigenic" in claim 60 is ambiguous and indefinite because the specification does not define the term "being particularly antigenic" and one of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The recitation of "humans are being treated" in claim 68 has no antecedent basis in base claim 51 because the base claim 51 recites the method wherein the "mucosal surface of the prospective mother is exposed to one or more antigens. Appropriate correction is required.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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14. Claims 50-60, 64-67, 70, 73, 77, 79, 81, 85, 86, 89, 90, 92 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; PTO 1449) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892).

The '825 patent teaches a method of treating infertility by administering TGF β , such as TGF β 1, TGF β 2, TGF β 3, and TGF β 4 (See column 5, line 9-11, in particular) along with antigens such as ovum, sperm on the surface or conceptus into the reproductive track (genital mucosal surface) of the a female to increase the success rate of implantation (See column 5 line 9-12, claim 4 of '825 patent, in particular). The reference TGF β may be administered either before, after or simultaneously with the male antigens such as the sperms of the prospective father which are known to express MHC class I molecule on the surface and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female (See claims 1-5; column 6 line 67 bridging column 7 line 23; column 4, line 12-21). The reference TGF β or analog may be administered by injection, patch, and gels that are slow release (See column 5, line 1-2; column 6, line 45-55). The '825 patent further teaches a method of diagnosing or testing the presence of active and/or immunological TGF β in female or diagnosing mammals with infertility due to inadequate TGF β (See column 6, line 8-16, column 3, lines 59-65, in particular). The reference method also can be used in conjunction with assisted reproduction such as IVF (See column 3 lines 66 bridging column 4, lines 6, in particular). The '825 patent teaches that TGF β stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular).

The claimed invention as recited in claim 50 differs from the teachings of the reference only that the method of eliciting symptoms of an infertility condition in a mammalian mother comprising exposing the prospective mother to one or more MHC Class I antigens of a prospective father to induce tolerance to said antigen or antigens.

The claimed invention as recited in claim 55 differs from the teachings of the reference only that the TGF β and the one or more antigens are administered at one site.

The claimed invention as recited in claim 56 differs from the teachings of the reference only that TGF β and the MHC Class I antigen or antigens are each administered at a first site and a different site respectively.

The claimed invention as recited in claim 66 differs from the teachings of the reference only that the one or more antigens are presented in purified or semi-purified form.

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The claimed invention as recited in claim 67 differs from the teachings of the reference only that the method include inert or adjuvant carriers.

The claimed invention as recited in claim 79 differs from the teachings of the reference only that the TGF β is administered in its active form.

The claimed invention as recited in claim 86 differs from the teachings of the reference only that the human beings are being treated and the exposure to TGF β and male antigen is a multiple exposure.

Clark *et al* teach that bioactive TGF β is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular).

Chaouat *et al* teach that immunizing female with the male leukocyte purified from spleen which carried the paternal MHC class I haplotype in a carrier such as PBS can lead to an increase protection during pregnancy (See abstract, Materials and Methods, in particular). Chaouat *et al* teach the protection is associated with active suppression against maternal cell-mediated immunity in the form of tolerance (See Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of administering TGF β , such as TGF β 1, TGF β 2, TGF β 3, and TGF β 4 (See column 5, line 9-11, in particular) along with the antigens such as ovum, sperm or leukocyte that expressed MHC class I molecule or conceptus as taught by the '825 patent with the method of immunizing female with paternal leukocyte antigen as taught by Chaouat *et al* and Feinberg *et al* for a method of inducing tolerance to paternal antigens to alleviate symptoms of infertility in a prospective mother as taught by the '825 patent, Clark *et al*, Chaouat *et al* and Feinberg *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '825 patent teaches that TGF β stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular). Chaouat *et al* teach that immunizing female with the male leukocyte which carried the paternal MHC class I haplotype can lead to protection of fetus from maternal cell-mediated immunity (See Abstract, in particular). Clark *et al* teach bioactive TGF β is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive

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activity that leads to induction of tolerance in vivo during the first trimester pregnancy in humans (See abstract, in particular). Claims 55-56 are included in this rejection because the recitation of administering systemically TGF β and one or more antigens or TGF β and one or more antigens each administered at a first site and a different site is an obvious variation of the teaching of the '825 patent since the '825 patent teaches that TGF β can be administered simultaneously, before or after the antigen and the sites of administration is within the purview of one ordinary skilled in that art at the time the invention was made. Claim 79 is included in this rejection because the recitation of active form is within the teachings of '825 patent because administering TGF β and antigens lead to increase the success rate of implantation, which is the active form of TGF β (See entire document, Claims of 825 patent, in particular). Claim 86 is included in this rejection because the recitation of multiple exposure to TGF β and male antigen is within the purview of one of ordinary skilled in the art based on the teachings of the '825 patent.

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 6/14/01 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claimed invention recites the administration of substantially purified exogenous TGF β to the mother prior to conception or to embryo transplantation. Clark teaches the up-regulation of TGF β post-implantation and does not definitely show any role prior to conception. Even if Clark had confirmed this proposed function of TGF β 2, this does not suggest the role of TGF β in seminal plasma. Clark does not disclose or suggest that the type and magnitude of the immune suppression caused by the TGF β prior to conception. Chaouat does not disclose or suggest that TGF β might play any role. Chaouat does not teach immunization with antigens such as MHC class I antigens would be useful for treatment of infertility. As discussed in the Clark declaration, Chaouat et al have reported that immunoprevention of spontaneous abortion in the mouse can occur when the treatment is given as late as 3 days after implantation. It would not have been obvious that TGF β treatment of preimplantation embryos would have any effect on the phenomena being investigated by Clark and by Chaouat. It was known from Clark et al that immunization of mice which prevented abortions increased the level of production of the novel TGF- β 2 since the novel TGF- β 2 like molecule described by Clark is not a conventional isoform of TGF- β .

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., prior to conception or to embryo implantation) are not recited in the rejected claim(s). Although the

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claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, none of the claims recites administering antigens prior to conception or to embryo implantation and the role of TGF β in seminal plasma. In fact, claim 59 recites antigens are administered first follows by administration of TGF β . The '825 patent teaches that TGF β may be administered either before, after or simultaneously with the male antigens such as the sperms of the prospective father which are known to express MHC class I molecule on the surface and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female (See claims 1-5; column 6 line 67 bridging column 7 line 23; column 4, line 12-21).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Chaouat *et al* teach immunizing female with the male leukocyte (paternal antigen) purified from spleen which carried the paternal MHC class I haplotype in a carrier such as PBS can lead to an increase protection during pregnancy (See abstract, Materials and Methods, in particular). In fact, the specification on page 8 at line 12 discloses that MHC antigens express on sperm cells and may include leukocytes, which are known to express MHC antigen.

In response to Applicants' argument that the novel TGF- β 2 like molecule in Clark *et al* is different from the conventional isoform of TGF β , and one would not have expected that administering a conventional TGF β isoform would prove beneficial in preventing infertility, the claims are not drawn to preventing infertility. Further, claims 75 and 76 recite TGF β is modified comprises substitution, deletion, or addition mutants or peptide fragments of TGF β which are clearly non-conventional TGF β .

15. Claims 66-67 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-60, 64-67, 70, 73, 77, 79, 81, 85, 86, 89, 90, 92 and 93 and further in view of Harlow *et al* (in A Laboratory Manual, Cold Spring Harbor Laboratory, page 61, 1988; PTO 892), World Health Organization (in World Health Organization Laboratory Manual for the

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Examination of Human Semen and Semen Cervical Mucus Interaction, Cambridge University Press, NY 1987, PTO 892) and Martin-Villa *et al* (Biol Reprod 55(3): 620-9, Sept 1996; PTO 892).

The combined teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claims 66-67 differs from the teachings of the references only by the recitation that one or more antigens are presented in purified or semi-purified form.

The claimed invention as recited in claim 71 differs from the teachings of the references only by the recitation that the exposure of one or more antigens is to the prospective mother's genital tract in the form of the prospective father's ejaculate, and the level of exposure is determined by the cell count and antigenic density on the surface of such cells.

Harlow *et al* teach a simple method of purifying any protein antigen by polyacrylamide gels electrophoresis (See page 61, in particular). Harlow *et al* having pure antigen provides the best case for the production of antibodies.

The WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining sperm count of a prospective father's ejaculate (See page 5, page 9, Counting the spermatozoa, in particular) and various methods of determining male infertility.

Martin-Villa *et al* teach a method of purifying sperm and determining antigen density such as HLA on cell surface using double labeling cytofluorometry and relevant antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA (See entire document, Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to purify antigen as taught by Harlow *et al* using the antigens from the sperm or conceptus as taught by the '285 patent or the semi-purify sperm antigens from the ejaculate by washing and counting as taught by the WHO Laboratory Manual for the Examination of Human Semen or the purified human spermatozoa from the prospective father's ejaculate and determining the antigen density by double labeling cytofluorometry and relevant antibody as taught by Martin-Villa *et al* to determine the levels of antigen prior to exposing the prospective mother's genital tract to one or more antigens to induce immune tolerance to the antigen(s) of the prospective father for a method of eliciting an immune reaction and alleviation of symptoms of

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infertility condition as taught by '825 patent, Clark *et al*, and Chaouat *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Harlow *et al* teach purifying any protein antigen by polyacrylamide gels electrophoresis is a simple method (See page 61, in particular). The WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining sperm count of a prospective father's ejaculate is useful for (See page 5, page 9, Counting the spermatozoa, in particular) determining male infertility. Martin-Villa *et al* teach a method of purifying sperm and determining antigen density such as HLA on cell surface using double labeling cytofluorometry using relevant antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA, as one of the indicator for male fertility (See entire document, Abstract, in particular).

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 6/14/01 have been fully considered but are not found persuasive.

Applicants' position is that the additional references cited by the Examiner in these items represent features which would only be obvious to combine with the administration of a TGF β in conjunction with an antigen on the prospective father as defined by amended claim 50.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., prior to conception or to embryo implantation) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, none of the claims recites administering antigens prior to conception or to embryo implantation and the role of TGF β in seminal plasma. In fact, claim 59 recites antigens are administered first follows by administration of TGF β . The '825 patent teaches that TGF β may be administered either before, after or simultaneously with the male antigens such as the sperms of the prospective father which are known to express MHC class I molecule on the surface and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female (See claims 1-5; column 6 line 67 bridging column 7 line 23; column 4, line 12-21).

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In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Chaouat *et al* teach immunizing female with the male leukocyte (paternal antigen) purified from spleen which carried the paternal MHC class I haplotype in a carrier such as PBS can lead to an increase protection during pregnancy (See abstract, Materials and Methods, in particular). In fact, the specification on page 8 at line 12 discloses MHC antigens expresses on sperm cells and may include leukocytes which are known to express MHC antigen.

In response to Applicants' argument that the novel TGF- β 2 like molecule in Clark *et al* is different from the conventional isoform of TGF β , and one would not have expected that administering a conventional TGF β isoform would prove beneficial in preventing infertility, the claims are not drawn to preventing infertility. Further, claims 75 and 76 recite TGF β is modified comprises substitution, deletion, or addition mutants or peptide fragments of TGF β which are clearly non-conventional TGF β .

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Clark *et al* teach bioactive TGF β is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular). Chaouat *et al* teach immunizing female with the male leukocyte purified from spleen which carried the paternal MHC class I haplotype in a carrier such as PBS can lead to an increase protection during pregnancy (See abstract, Materials and Methods, in particular) and the protection is associated with active suppression against maternal cell-mediated immunity in the form of tolerance (See Abstract, in particular). The '825 patent teaches a method of treating infertility by administering TGF β , such as TGF β 1, TGF β 2, TGF β 3, and TGF β 4 (See column 5, line 9-11, in particular) along with antigens such as ovum, sperm on the surface or conceptus into the reproductive track (genital mucosal surface) of the a female to

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increase the success rate of implantation (See column 5 line 9-12, claim 4 of '825 patent, in particular).

16. Claims 75 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-60, 64-67, 70, 73, 77, 79, 81, 85, 86, 89, 90, 92 and 93 and further in view of Tuan *et al* (Connect Tissue Res 34(1): 1-9, 1996; PTO 892) or Lyons *et al* (J Cell Biol 110(4): 1361-7, April 1990; PTO 892).

The combined teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claim 75 differs from the teachings of the references only by the recitation that the TGF β is modified.

The claimed invention as recited in claim 76 differs from the teachings of the references only by the recitation that the modified TGF β wherein the modification comprises substitution, deletion, or addition mutants or peptide fragments of TGF β .

Tuan *et al* teach modified TGF β and analog of TGF β such as TGF β 1-1 and TGF-B1-F2 fusion proteins from *E coli*; the reference modified TGF β and analog has comparable antiproliferative activity to purified platelet TGF-beta 1 (See abstract, in particular).

Lyons *et al* teach peptide fragment of TGF β such as N terminal deletion using plasmin or acid activation and the resulting peptide fragment of TGF β is active (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TGF beta as taught by the '825 patent for the modified TGF β analog as taught by Tuan *et al* or the active fragment of TGF β as taught by Lyons *et al* for a method of eliciting an immune reaction in a prospective mammalian mother by exposing said prospective mother to one or more antigens of said prospective father and substantially purified TGF β , said mother leading to tolerance to one or more antigens and alleviation of symptoms of infertility condition as taught by '825 patent, Clark *et al*, and Chaouat *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Tuan *et al* teach modified TGF β and analog of TGF β has

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comparable antiproliferative activity to purified platelet TGF-beta 1 (See abstract, in particular). Lyons *et al* teach peptide fragment of TGFβ such as active TGFβ by N terminal deletion can be activated by plasmin or acid activation (See abstract, in particular).

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 6/14/01 have been fully considered but are not found persuasive.

Applicants' position is that it would not have been obvious to utilize the references for the purposes stated by the Examiner without knowing of the present invention as defined in Claim 50.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

17. Claims 83-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-62, 64-67, 70, 73, 77, 79, 81, 89, 90, 92 and 93 and further in view of Grainger *et al* (Nat Med 1(9): 932-7, Sep1995; PTO 892).

The combined teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claim 83 differs from the teachings of the references only by the recitation that the method of treating includes administration of plasmin as to increase the level of active TGFβ.

The claimed invention as recited in claim 84 differs from the teachings of the references only by the recitation that the TGFβ is administered in an unpurified form using a biological source rich in TGFβ.

The claimed invention as recited in claim 85 differs from the references only by the recitation that the TGFβ is administered in the form of platelets.

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Grainger *et al* teach transforming growth factor beta 1 (TGF-beta 1) is a platelet-derived cytokine and human whole platelets is a rich source of inactive TGF-beta 1, which can be activate by plasmin (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the active TGF beta as taught by the '825 patent for the unpurified form using a biological source rich in TGF β such as the platelets along with plasmin to activate the inactive form of TGF β as taught by Grainger *et al* for a method of eliciting an immune reaction in a prospective mammalian mother comprising exposing said prospective mother to one or more antigens of said prospective father and substantially purified TGF β , said mother leading to tolerance to one or more antigens and alleviation of symptoms of infertility condition as taught by '825 patent, Clark *et al*, and Chaouat *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Grainger *et al* teach platelet is a rich of inactive TGF β and which can be activate by plasmin (See abstract, in particular).

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 6/14/01 have been fully considered but are not found persuasive.

Applicants' position is that the examiner's reliance on these references is completely inconsistent with the enablement rejection under 112 in relation to fragments and analogous and other modification of TGF beta. It would not have been obvious to utilize the references of Grainger *et al* for the purposes stated by the Examiner without knowing of the present invention as defined in Claim 50.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

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18. Claim 92 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-62, 64-67, 70, 73, 77, 79, 81, 89, 90, 92 and 93 and further in view of Heidenreich *et al* (Am J Reprod Immunol 31(2-3): 69-76, Mar-Apr 1994; PTO 892).

The combined teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claim 92 differs from the teaching of the references only by the recitation that the method includes testing whether anti-sperm antibodies exist.

Heidenreich *et al* teach a method of detecting anti-sperm antibody in infertile male using a highly sensitive and reproducible ELISA assay (See abstract, in particular). The reference assay synchron ELISA (Synelisa) is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the step of diagnosing whether anti-sperm antibodies exist using the assay as taught by Heidenreich *et al* with the method of treating infertility by administering TGF β and male antigens as taught by the '825 patent, Clark *et al*, and Chaouat *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Heidenreich *et al* teach anti-sperm antibody is associated with male infertility and the reference assay is useful for is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 6/14/01 have been fully considered but are not found persuasive.

Applicants' position is that the examiner's reliance on these references is completely inconsistent with the enablement rejection under 112 in relation to fragments and analogous and other modification of TGF beta. It would not have been obvious to utilize the references of Heidenreich *et al* for the purposes stated by the Examiner without knowing of the present invention as defined in Claim 50.

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In response to applicant's argument that this rejection is completely inconsistent with the enablement rejection under 112 in relation to fragments and analogous and other modification of TGF beta, art rejection is completely separate from the enablement and written description rejections under 35 USC 112 first paragraph.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

19. Claims 68-69, 87-88 and 91 stand free of art.
20. No claim is allowed.
21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

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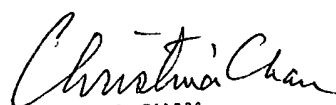
22. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

March 10, 2003


CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600